EDITORIALS

Revisiting the drug interaction between tamoxifen and SSRI antidepressants

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Women taking tamoxifen should play safe and avoid antidepressants that inhibit CYP2D6

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Few topics in therapeutics are more vexing than drug interactions. They number in the thousands, involve confusing terminology, and are rarely supported by evidence stronger than case reports and volunteer studies.¹ It's not surprising, therefore, that experts disagree on which interactions are serious and which ones are not.² And yet their importance is undeniable because they can cause serious morbidity or even death, despite epitomizing, in theory at least, avoidable drug related harm.

Over the past decade, few drug interactions have been as controversial as those involving tamoxifen and selective serotonin reuptake inhibitor (SSRI) antidepressants,³ explored yet again by Donneyong and colleagues in a linked study (doi:10.1136/bmj.i5014).⁴ On its surface, the issue seems straightforward: as a prodrug, tamoxifen requires conversion to active metabolites, the most important of which is endoxifen. This process is influenced by cytochrome-P450 isoenzyme 2D6 (CYP2D6), an enzyme characterized by marked variability from person to person. Some SSRIs but not others inhibit CYP2D6, conceivably attenuating or even abolishing the benefits of tamoxifen.

The importance of this potential interaction is amplified by three factors. First, tamoxifen is a monumental treatment, conferring dramatic reductions in breast cancer recurrence and associated mortality.⁵ Second, antidepressants are often co-prescribed with tamoxifen for extended periods,⁶ in part because depression often coexists with breast cancer and in part to offset vasomotor symptoms induced by tamoxifen.⁷ Third, and in contrast with most drug interactions, the consequences are delayed by years and manifest simply as treatment failure, undermining causal attribution at the patient level.

Why does the interaction between tamoxifen and SSRIs remain controversial? One reason is that tamoxifen's pharmacokinetic fate involves processes other than CYP2D6.⁸ Another is that studies of the relation between CYP2D6 activity and outcomes in women receiving tamoxifen yield remarkably inconsistent results.⁹ Finally, with some exceptions,^{10 11} observational studies

show little evidence that use of antidepressants is associated with adverse outcomes in women receiving tamoxifen.¹²⁻¹⁴

Donneyong and colleagues used data from five US health insurance databases to study women already being treated with an SSRI at the outset of treatment with tamoxifen or who received an SSRI later during its course.⁴ Over a median follow-up of about two years, they found no difference in overall mortality among women receiving SSRIs that inhibit CYP2D6 (paroxetine and fluoxetine) relative to SSRIs that do not (citalopram, escitalopram, fluvoxamine and sertraline).

These findings are unsurprising, if for no other reason than follow-up was too brief for any differential survival to show up.⁵ Studying total mortality rather than cancer specific outcomes further diminished the investigators' ability to discern signal from noise. Consequently, this study does little to disprove a meaningful interaction between tamoxifen and CYP2D6 inhibitors. It does, however, illustrate just how challenging such studies can be. Pharmacoepidemiology is a relative newcomer to the science of drug interactions, with most studies exploring short term toxicities after the co-prescription of drugs with well established interactions.¹⁵⁻¹⁷ In contrast, the interaction between tamoxifen and CYP2D6 inhibiting SSRIs is characterized by an elusive outcome (treatment failure), a long latent period, and many other factors (including non-adherence, therapeutic switching, CYP2D6 polymorphisms, dose-response effects,¹⁸ variable mechanisms and degrees of inhibition,¹⁹ and a probable endoxifen threshold below which treatment failure is more likely²⁰) that collectively attenuate any signal that might exist. For these reasons, the tamoxifen-SSRI interaction is perhaps the most difficult drug interaction to explore using the techniques of pharmacoepidemiology.

Where does this leave patients and clinicians? In my view it is premature to dismiss an interaction between tamoxifen and SSRIs, particularly given the stakes and the ease with which harm can be mitigated. We know tamoxifen prevents recurrence and death from breast cancer,⁵ that endoxifen is its dominant metabolite, and that CYP2D6 plays an important role in its

generation. These observations alone make it difficult to justify the extended co-prescription of tamoxifen with strong CYP2D6 inhibitors. We also know that switching antidepressants can result in markedly higher endoxifen concentrations.²¹ Not only is this intuitively desirable, it affords clinicians and patients some therapeutic leeway.

I suggest the co-prescribing of antidepressants and tamoxifen be guided by three principles. First, antidepressants should be selectively prescribed to patients likely to benefit. This is plainly true of all treatments, but it warrants explicit mention here in view of the limited utility of SSRIs in people with mild to moderate depression.²² Second, controversy notwithstanding, pragmatism dictates preferential avoidance of antidepressants known to inhibit CYP2D6, including fluoxetine, duloxetine, bupropion, and especially paroxetine.²³ Sertraline, citalopram, escitalopram, and venlafaxine impart lesser degrees of inhibition and are reasonable alternatives. Finally, for women already taking tamoxifen with a known CYP2D6 inhibitor, any change in treatment should be gradual to minimize the risks of SSRI withdrawal and the idiosyncratic adverse effects commonly seen on initiation of treatment.

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